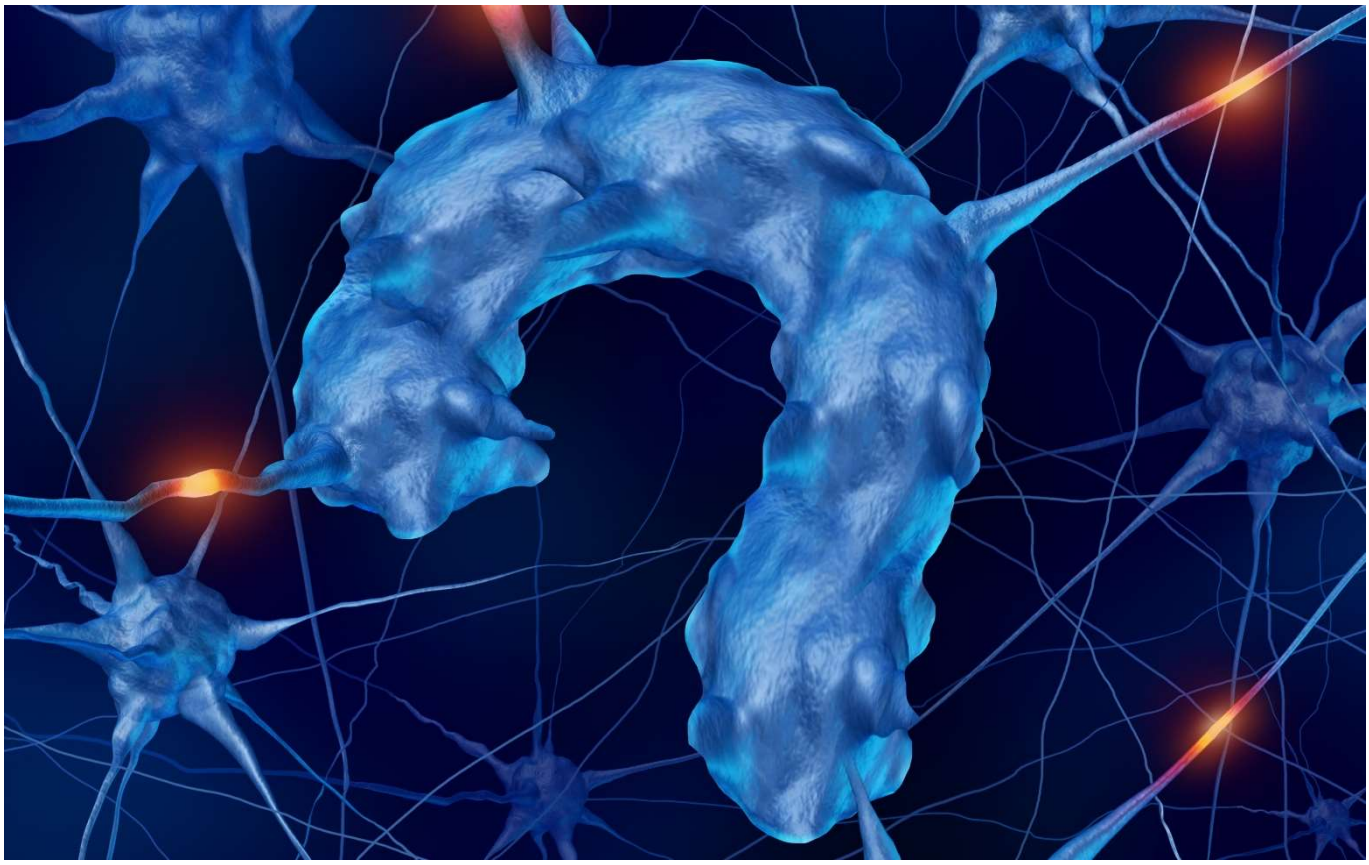

MULTIPLE SCLEROSIS IN CHILDREN – A CURRENT REVIEW

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ABSTRACT

Multiple sclerosis is a progressive, demyelinating disease of the central nervous system, characterised by the occurrence of multifocal and multiperiodic lesions in the brain and the spinal cord. The spectrum of symptoms may include disorders of: eye, sphincter's control, motor coordination, exteroceptive sensation, paresis of the limbs and cognitive impairment. Children accounts for 2-4% of all MS patients. Boys are affected by the disease slightly more often (1:0.8 in relation to girls), however, in children above six years of age, this trend begins to reverse and in group above ten years of age, girls are affected more than twice as often as boys. The etiology of MS is not sufficiently known. Combination of environmental, genetic and autoimmune factors is postulated. It has been proven that in children with already diagnosed MS antibodies against EBV are detected more frequently. There was no correlation with vaccinations found. There are four forms of classical MS: relapsing-remitting, secondary progressive, primary progressive and progressive relapsing. In children, relapsing-remitting form is the most often. Relapses at the beginning of the disease are more frequent than in adults, but neurological changes almost always withdraw. Diagnosis is primarily based on McDonald's criteria. Changes in the brain in younger children found in MRI are usually larger, less sharply demarcated, confluent, but may regress. As in adults, the corticosteroids are used to suppress the relapse. Complementary symptomatic treatment is rarely used and a well-chosen rehabilitation is preferred. Disease modifying drugs that are well tolerated by children are interferon ß and glatiramer acetate. There are limited data from clinical trials on the use of second-line drugs in children.

BACKGROUND

Multiple sclerosis is a progressive, demyelinating disease of the central nervous system (CNS), whose etiology is not fully understood. It is characterised by the occurrence of multifocal and multiperiodic lesions in the brain and the spinal cord, which lead to neurological disorders of varied profile and severity. Depending on the localization of the ongoing demyelinating process, the spectrum of symptoms may include disorders of: eye (among others: optic neuritis, nystagmus, diplopia); sphincters' control; motor coordination (cerebellar ataxia); exteroceptive sensation; as well as paresis of the limbs and cognitive impairment. The peak of the disease occurs in the third and fourth decades of life. There are four main types of multiple sclerosis: relapsing-remitting, secondary progressive, primary progressive and progressive relapsing, which differ in clinical manifestation and treatment strategies [1, 2].

Children accounts for 2-4% of all MS patients, although according to some reports, even more than 10% of adult MS patients experienced the first symptoms in childhood. Among younger children, boys are affected by the disease slightly more often (1:0.8 in relation to girls), however, in children above six years of age, this trend begins to reverse and in group above ten years of age, girls are affected more than twice as often as boys [3].

ETIOLOGY

The etiology of multiple sclerosis is not sufficiently known. Combination of environmental, genetic and autoimmune factors is postulated. However, there are several factors that increase the risk of developing the disease in children. For example, it has been proven that in children with already diagnosed multiple sclerosis antibodies against the EBV virus are detected more frequently [3]. There was no correlation found with CMV, HSV, VZV or B19 parvovirus infection, nor was there any relationship between MS incidence and vaccinations, although there are studies suggesting a more frequent history of infection or vaccinations before the first onset of clinical syndrome of neurological symptoms in patients with early-onset MS (before 12 years of age), which, however, requires further research [3, 4]. There seems to be a correlation between the higher prevalence of MS in children and exposure to tobacco smoke (passive smoking) and the occurrence of HLA-DRB1 haplotype in the major histocompatibility complex. However, the effect of vitamin D3 deficiency in children on the development of the disease is unknown (unlike adults in whom it is a proven risk factor), although it is also a fact that this deficiency is detected in 2/3 of children with multiple sclerosis [3, 4].

Increasingly, attempts are being made to examine the relationship between the composition of the intestinal flora and the course of MS. A Canadian study from 2016 indicates that in children with already diagnosed multiple sclerosis, in which the representation of bacteria of the *Fusobacterium* genus was less significant, there was a greater risk of a more immediate relapse of the disease [5].

NATURAL COURSE OF THE DISEASE

There are four forms of classical multiple sclerosis:

- relapsing-remitting;
- secondary progressive - as a consequence of the relapsing-remitting form, with a permanent deterioration of the neurological state;
- primary progressive - from the beginning of the disease a gradual deterioration of the patient's condition is observed;
- progressive relapsing.

In addition, the SM variants are also distinguished:

- Devic's disease (inflammation of the spinal cord and optic nerves);
- Marburg disease (in which the disease progresses rapidly in weeks or even days);
- Baló concentric sclerosis;

and Schilder's multiple sclerosis [6, 7].

In children, relapsing-remitting form is the most often one. Relapses at the beginning of the disease are more frequent than in adults, but neurological changes almost always withdraw [3, 8], although a Turkish study of 193 children from June 2017 indicates that in children with MS of early onset (below 12 years of age) the intervals between relapses were longer than in the older children at the time of the first clinical manifestation, although at the same time the attacks gave more serious neurological symptoms [4]. The occurrence of the primary progressive form is associated with poor prognosis as to the physical development of the child [8].

The most common symptoms of multiple sclerosis are optic neuritis, epileptic seizures, sensory disturbances and vertigo [8]. In more than half of the patients, the first manifestation of the disease is multisymptomatic and most often includes brainstem syndromes, sensation disorders, motor disorders and optic neuritis. Facial neuritis, epileptic seizure or neuromyelitis optica are rarer at the beginning of the disease [4]. Psychiatric disorders (especially affective disorders), increased fatigue, cognitive impairment and learning difficulties may also occur in the course of the disease, although learning difficulties are often associated not so much with cognitive impairment as rather with frequent school absence, affective disorders and chronic fatigue [3].

Retrobulbar optic neuritis may be the first manifestation of multiple sclerosis and always requires neurological consultation. Although this condition occurs in children less often than in adults, it should be remembered that it is present in 1/4 cases of acute demyelinating syndromes in children. Optic neuritis in children occurs bilaterally more often than in adults. However, despite frequent association with MS, it is not a pathognomonic symptom of this disease; it can also occur in some neuroinfections, as a very rare side effect of vaccination or in the course of neuromyelitis optica. Symptoms of retrobulbar optic neuritis usually disappear completely within a few weeks [9].

DIAGNOSIS

In children, as in adults, diagnosis is primarily based on McDonald's criteria that allow the disease to be

diagnosed according to only clinical symptoms if at least two relapses occurred and there are objective clinical data indicating presence of at least two foci of demyelination. If any of these conditions are not met, the McDonald criteria enable diagnosis of the disease depending on the result of magnetic resonance imaging in T2-weighted images. The changes that can be detected in MRI are periventricular changes, cortical changes, changes located in the brainstem, cerebellum and spinal cord [4]. Changes in the brain in younger children are usually larger, less sharply demarcated, confluent, but may regress, unlike changes in older children [3]. In turn, functional MRI allows for the observation of decreased recruitment response of some areas of the cerebral cortex in children with MS in relation to healthy people (especially in the parietal and occipital lobe), which can explain cognitive impairment in these children [10].

Significant tests in the diagnosis of multiple sclerosis are the examination of visual evoked potentials (the result of this examination may be abnormal even in the absence of optic neuritis) and test for the presence of oligoclonal bands in the cerebrospinal fluid [3, 4].

TREATMENT

As in adults, the corticosteroids (prednisone or methylprednisolone) are used to suppress the relapse. Complementary symptomatic treatment is rarely used and a well-chosen rehabilitation is preferred. Disease modifying drugs that are well tolerated by children are interferon ß and glatiramer acetate. There are limited data from clinical trials on the use of second-line drugs in children (e.g. rituximab or mitoxantrone), hence they should not be routinely used in this age group [3].

CONCLUSIONS

Children are a small group among patients with multiple sclerosis, however, one should always take this unit into account in the differential diagnosis when the patient has a set of neurological symptoms indicating the dissemination of the pathological process in time or space. The progression of multiple sclerosis in children seems to be in many aspects lighter than in adults, but the early onset of the disease is associated with a higher risk of cognitive and mobility impairment in adulthood [11]. The hope for a more accurate diagnosis of this disease (of still unrecognized etiology) which is relatively rare in children, is particularly raised by modern methods of neuroimaging and the development of molecular diagnostics and genetic research. In the first-line therapy, interferon ß and glatiramer acetate should be used as in adults. Further research is needed on the safety and validity of second-line therapy in children, including monoclonal antibodies.

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